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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,344	04/08/2002	Irving Wainer	1908-006-27	3873

7590 05/23/2005

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EXAMINER	
GABEL, GAILENE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,344	WAINER ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☒ Claim(s) *1-10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/8/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims Under Examination

1. Claims 1-10 are pending and are currently under examination.

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior applications in the first sentence of the specification or in an application data sheet by identifying the prior application by application number (37 CFR 1.78(a)(2) and (a)(5)). If the prior application is a non-provisional application, the specific reference must also include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

In this case, this 371 National Stage application claims the benefit of provisional application number 60/151,402 but fails to contain a specific reference thereto in the first sentence of the specification.

Trademark Usage

3. The use of the trademarks such as "Superdex 200, Sephadex G50, CHAPS" and others, has been noted in this application. They should be capitalized wherever they appear and be accompanied by their generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Specification

4. 35 U.S.C. 112, first paragraph, requires the specification to be written in "full, clear, concise, and exact terms." The specification is replete with abbreviations, which do not appear to be adequately defined. The specification should be revised carefully in order to comply with 35 U.S.C. 112, first paragraph. Examples of some abbreviations used in the specification, which have not been defined are "MSD", "EDTA", "TAX", and "ADR". Appropriate correction is required.

5. The disclosure is objected to because of the following informalities:

- in page 13, line 19, "chromato-graphed" should be --chromatographed--.

- in page 13, lines 23 and 24, "co-operative" should be --cooperative-- in all three occurrences.

Appropriate correction is required.

Claim Objections

6. Claims 1-10 are objected to because of the following informalities:

- in the preamble and step (i) of claim 1, the term "p-glycoprotein" should be "P-glycoprotein".

- in claims 2-10, "Claim" should be --claim--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing because it is unclear what structural and functional cooperative relationship exists between the recitation of "a liquid chromatographic system" in step (ii) and the recitation of "a liquid chromatography system" in step (i). If Applicant intends that "a liquid chromatographic system" in step (ii) is the same element as that recited in step (i), then the recitation of "a liquid chromatographic system" in step (ii) has improper antecedent basis problem. Alternatively, if Applicant refers to two distinct elements for each occurrence of "liquid chromatographic system" in each of steps (i) and (ii) which seems to be the case, then claim 1 is indefinite and confusing in using a same terminology to refer to two distinct elements in the claim. In this case, "liquid chromatography system" in step (i) appears to refer to a device which is on-line with the membrane support whereas the recitation of "liquid chromatographic system" in step (ii) appears to intend a solution mixture containing ligands that is flowed through,

i.e, continuously contacted with, the device for specific interaction with P-glycoprotein. Please clarify.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In this case, the preamble recites, "A method for identifying, isolating, and characterizing ligands that interact with P-glycoprotein"; however, there are no method steps recited thereafter in the claim which would otherwise provide how to differentially or selectively identify (detect ligand binding using a label), isolate (separate by capturing and eluting ligands, or characterize (evaluate structural information or interaction), the ligands that interact with P-glycoprotein, as required by the preamble.

Claim 3 lacks clear antecedent basis in reciting, "the elution profile."

Claim 4 is vague and indefinite in relation to claim 1 from which it depends in reciting, "an identified ligand" because it is unclear as recited, how a ligand is identified or how an identified ligand is obtained from those recited in claim 1; hence, the recitation of "identified ligand" lacks clear antecedent basis. Does Applicant intend that a binding interaction takes place between ligands and the immobilized P-glycoprotein and that ligands that bind the immobilized P-glycoprotein, are selected as the "identified ligands"? Accordingly, it is unclear how the "identified ligand" relates structurally or functionally with the ligands recited in claim 1.

Claim 5 is vague and indefinite in relation to claim 1 from which it depends in reciting, "an identified ligand" because it is unclear as recited, how a ligand is identified or how an identified ligand is obtained from those recited in claim 1; hence, the

recitation of "identified ligand" lacks clear antecedent basis. Does Applicant intend that a binding interaction takes place between ligands and the immobilized P-glycoprotein and that ligands that bind the immobilized P-glycoprotein, are selected as the "identified ligands"? Accordingly, it is unclear how the "identified ligand" relates structurally or functionally with the ligands recited in claim 1.

Claim 6 is indefinite in reciting, "PGP". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 6 is indefinite because it is unclear how the method of claim 1 is used "to continuously identify ligands that specifically bind P-glycoprotein by displacement competition binding assay". Does Applicant intend that a displacement competitive binding interaction takes place between ligands and the compounds for binding with immobilized P-glycoprotein and that ligands that displace the compounds for binding the immobilized P-glycoprotein, are identified as the compounds, i.e. for treating MDR1/PGP? Accordingly, it is unclear how the "ligands [identified]" relate structurally or functionally with those ligands recited in claim 1.

Claim 6 provides for the use of the method of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 7 is vague and indefinite in relation to claim 1 from which it depends in reciting, "an identified ligand" because it is unclear as recited, how a ligand is identified

or how an identified ligand is obtained from those recited in claim 1; hence, the recitation of identified ligand lacks clear antecedent basis. Does Applicant intend that a binding interaction takes place between ligands and the immobilized P-glycoprotein and that ligands that bind the immobilized P-glycoprotein, are selected as the "identified ligands"? Accordingly, it is unclear how the "identified ligand" relates structurally or functionally with the ligands recited in claim 1.

Claim 7 is vague and indefinite in relation to claim 1 from which it depends in reciting, "an eluate containing said ligand" because it is unclear how the "eluate containing said ligand" relates structurally or functionally with the elements recited in claim 1. Specifically, claim 1 recites that it is the liquid chromatographic system that contains the ligands. Please clarify.

Regarding claim 7, the phrase "another testing device" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "another testing device"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim 9 is indefinite in reciting, "MDR1/PGP". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 9 is vague and indefinite because it is unclear how the method of claim 1 is used to identify compounds for treating MDR1/PGP. Does Applicant intend that a binding interaction takes place between ligands and the immobilized P-glycoprotein and that ligands that bind the immobilized P-glycoprotein, are identified as the compounds

for treating MDR1/PGP? Accordingly, it is unclear how the "compounds [identified]" relate structurally or functionally with the ligands recited in claim 1.

Claim 9 provides for the use of the method of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 10 is vague and indefinite because it is unclear how the "more than one chromatographic ... columns" recited in the instant claim relate to the "liquid chromatographic system" recited in claim 1 from which it depends. Perhaps, Applicant intends that the chromatography system in claim 1, step (i) comprises more than one chromatographic column.

Claim 10 is vague and indefinite because it is unclear what the "P-glycoprotein-containing compounds or derivatives" are (structurally and functionally), in relation to the P-glycoproteins immobilized in claim 1 from which claim 10 depends. Perhaps, Applicant intends "different P-glycoprotein derivatives immobilized ...".

Claim 10 is indefinite and confusing in reciting, "The method of claim 1, which comprises more than one chromatographic screen using columns comprising different P-glycoprotein-containing compounds or derivatives" because claim 10 appears to intend reciting a method step that further comprises the steps set forth in claim 1 but fails to do so. It seems to recite limitations drawn to a product or apparatus. Additionally, it is unclear as to whether the "chromatographic columns" in the instant

claim is the same as the "chromatographic system" in claim 1 or if they are different, how they relate to each other. Perhaps, Applicant intends, "The method of claim 1, wherein the liquid chromatography system further comprises more than one chromatographic columns on-line with artificial membrane supports having different P-glycoprotein derivatives immobilized thereon, for screening of different ligands or compounds that bind the different P-glycoprotein derivatives" or similar language.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Artificial membranes are known in the art to refer to monolayers of phospholipid molecules covalently bonded to silica particles which have been used to purify membrane proteins relevant to drug discovery.

8. Claims 1-3, 7, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ambudkar et al. (Partial purification and reconstitution of the human multi-drug resistance pump: Characterization of the drug-stimulatable ATP hydrolysis, Proc. Natl. Acad. Sci., Vol. 89, pages 8472-5476 (September 1992)) in view of Yang et al. (Immobilized Artificial Membranes – screens for drug membrane interactions, Advanced Drug Delivery Review, Vol. 23, pages 229-256 (1996)).

Ambudkar et al. teach immobilizing P-glycoprotein on artificial membrane support. Ambudkar et al. found that when immobilized in artificial membrane, P-glycoprotein catalyzes drug-stimulated ATP hydrolysis and ATP-dependent efflux of drugs and established that P-glycoprotein is an ATP-dependent multidrug transporter for multidrug-resistant human tumor cells. Specifically, Ambudkar et al. teach partially purifying P-glycoprotein, then immobilizing or embedding (reconstituting) the P-glycoprotein onto the artificial membrane support (proteoliposomes or phospholipid monolayer of vesicles) (see Abstract, page 8472, column 2, first full paragraph, and page 8473, column 1, second full paragraph (Reconstitution of P-glycoprotein)). The artificial membrane support having the P-glycoprotein immobilized thereto is contacted with one or more ligands (vinblastine, doxorubicin, daunomycin, actinomycin D, verapamil, and colchicine) after which the ligands are characterized by their specific interaction, i.e. stimulatory effect and relative potencies, with the P-glycoprotein (see

page 8474, column 1, second full paragraph to page 8475, column 1). Hence, Ambudkar et al. specifically provide that purification and functional immobilization , i.e. reconstitution, of P-glycoprotein into artificial membrane is essential in establishing its role as ATP-dependent multidrug transporter. Ambudkar et al. suggest that artificial membrane system having P-glycoprotein immobilized thereto, should prove useful for drug transport studies for screening potential drugs and ligand substrates for multidrug resistant human tumor cells (see page 8476, column 1, second full paragraph).

Ambudkar et al. differ from the instant invention in failing to teach placing the artificial membrane support on-line with a liquid chromatography system.

Yang et al. teach immobilized artificial membranes (IAM) on-line with chromatographic systems (see Abstract). Specifically, Yang et al. teach continuously adding one or more ligands (drugs) through IAM chromatographic columns in a chromatography system and identifying, isolating, and characterizing drugs that bind to the membrane interfaces (see page 238, column 1, first full paragraph to page 239, column 1). The ligands are eluted (partitioned), evaluated for their elution profile, i.e. partition coefficients, and evaluated for their effects on cells in vitro (see page 239, column 2, fourth full paragraph to page 245, column 2). The ligands identified by solute molecules that bind IAM are characterized using different, i.e. another, testing devices (^{31}P-Nuclear Magnetic Resonance Spectroscopy) (see page 249, last full paragraph to page 252, column 1). Yang et al. further teach using more than one chromatographic columns for screening different (more than one) ligands (see Figure 15). According to Yang et al., multiple drug transport pathways through cell membranes is essential in

drug screening/discovery, and provide that IAMs are useful in drug-membrane partitioning (see column 1, and page 231, column 1, first full paragraph). Yang et al. also provide that IAM chromatography is successful and useful in studies of drug permeability to cells.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the artificial membrane support having P-glycoprotein immobilized thereto as taught by Ambudkar, into the immobilized artificial membrane (IAM)-chromatography systems as taught by Yang because Yang specifically taught application of immobilized artificial membranes with liquid chromatography columns for use in obtaining critical information necessary for drug screening and drug discovery systems. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the artificial membrane support having P-glycoprotein immobilized thereto as taught by Ambudkar into the IAM-liquid chromatography system as taught by Yang because Ambudkar specifically taught that ATP hydrolysis and drug transport are directly mediated by P-glycoprotein in multidrug-resistant human tumor cells; hence, a screen for ligands that manifest themselves as good substrates or bad substrates for P-glycoprotein in multidrug-resistant tumor cells in immobilized artificial membrane as taught by Ambudkar and incorporated into IAM-chromatography as suggested by Yang (see page 233 and Abstract) is useful in providing information on solute partitioning, drug permeability, drug intestinal absorption, brain uptake, and skin permeability of specific myriad of drugs analyzed in a chromatographic system.

9. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ambudkar et al. (Proc. Natl. Acad. Sci., Vol. 89, pages 8472-5476 (September 1992)) in view of Yang et al. (Advanced Drug Delivery Review, Vol. 23, pages 229-256 (1996)) as applied to claims 1-3, 7, 9, and 10 above, and in further view of Kubota et al. (Pirarubicin Might Partly Circumvent the P-Glycoprotein-Mediated Drug Resistance of Human Breast Cancer Tissues, Anticancer Research Vol. 18, pages 967-972 (1998)).

Ambudkar et al. and Yang et al. have been discussed supra. Ambudkar et al. and Yang et al. differ from the instant invention in failing to teach evaluating a ligand obtained using the method of claim 1, to determine its effect on breast cancer cells in vitro.

Kubota et al. evaluated breast cancer cells for P-glycoprotein expression and in vitro chemosensitivity using doxorubicin, pirarubicin, adriamycin, and epirubicin. Kubota et al. found that the human breast cancer cells were in vitro sensitive at cut-off concentration of the drugs and with overall efficacy rates of 61%, 49%, and 79% for doxorubicin, epirubicin, and adriamycin, respectively (see Abstract and Table 1 in page 969, column 2).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Kubota in determining effects of specific ligands on human breast cancer cells, into the method of Ambudkar as modified by Yang wherein P-glycoprotein is immobilized into IAM on-line with chromatography because Kubota specifically taught that different drugs have different effects mediated

by P-glycoprotein in human breast cancer cells; hence, a screen for ligands that manifest themselves as good substrates or bad substrates for P-glycoprotein in multidrug-resistant human breast cancer cells in immobilized artificial membrane as taught by Ambudkar and incorporated into IAM-chromatography as suggested by Yang should prove useful in providing information on solute partitioning, drug permeability, drug intestinal absorption, brain uptake, and skin permeability between different myriad of drugs analyzed in a chromatographic system for interaction with human breast cancer cells.

10. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ambudkar et al. (Proc. Natl. Acad. Sci., Vol. 89, pages 8472-5476 (September 1992)) in view of Yang et al. (Advanced Drug Delivery Review, Vol. 23, pages 229-256 (1996)) as applied to claims 1-3, 7, 9, and 10 above, and in further view of Muzzammil et al. (99Tcm-sestamibi imaging of inhibition of the multidrug resistance transporter in a mouse xenograft model of human breast cancer, Nuclear Medicine Communications, 20 (2): 115-122 (February 1999) Abstract).

Ambudkar et al. and Yang et al. have been discussed supra. Ambudkar et al. and Yang et al. differ from the instant invention in failing to teach evaluating a ligand obtained using the method of claim 1, in an animal xenograft model of human breast cancer.

Muzzammil et al. teach evaluating P-glycoprotein inhibition by two potent chemosensitizers, PSC833 and GG918, in a mouse xenograft model of multi-drug resistant human breast cancer, MCF7-AdrR (see Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Muzzammil of evaluating P-glycoprotein inhibition in a mouse xenograft model of multi-drug resistant human breast cancer, into the method of Ambudkar as modified by Yang wherein P-glycoprotein is immobilized into IAM on-line with chromatography because Muzzammil specifically taught that different drugs have different effects mediated by P-glycoprotein in a mouse xenograft model of multi-drug resistant human breast cancer; hence, a screen for ligands that manifest themselves as good substrates or bad substrates for P-glycoprotein in immobilized artificial membrane as taught by Ambudkar and incorporated into IAM-chromatography as suggested by Yang should prove useful in providing information on solute partitioning, drug permeability, drug intestinal absorption, brain uptake, and skin permeability between different myriad of drugs analyzed in a chromatographic system for interaction with human breast cancer cells from a xenograft model.

9. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ambudkar et al. (Proc. Natl. Acad. Sci., Vol. 89, pages 8472-5476 (September 1992)) in view of Yang et al. (Advanced Drug Delivery Review, Vol. 23, pages 229-256 (1996)) as applied to claims 1-3, 7, 9, and 10 above, and in further view of Popkov et al. (Multidrug-

resistance drug-binding peptides generated by using a phage display library (Eur. J. Biochem., Vol. 251, pages 155-163 (1998)).

Ambudkar et al. and Yang et al. have been discussed supra. Ambudkar et al. and Yang et al. differ from the instant invention in failing to teach that the immobilized P-glycoprotein is complexed with a compound that specifically binds P-glycoprotein and using a displacement competition binding assay to continuously identify ligands that bind P-glycoprotein.

Popkov et al. teach generating P-glycoprotein functional analogs and analyze their interactions with multidrug-resistance drugs in a displacement competitive binding assay (see page 155, column 2, last full paragraph to page 156, column 1; page 156, column 2, third full paragraph under Competitive Displacement Assay; and page 158, column 1, first full paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Popkov of evaluating P-glycoprotein interactions in a displacement competitive binding assay, into the method of Ambudkar as modified by Yang wherein P-glycoprotein is immobilized into IAM on-line with chromatography because Popkov specifically taught that displacement competitive binding assay provides binding interaction information between different drugs and P-glycoprotein; hence, competitive binding assay for application in screening for ligands that manifest themselves as good substrates or bad substrates for P-glycoprotein in immobilized artificial membrane as taught by Ambudkar and incorporated into IAM-

chromatography as suggested by Yang should prove useful in providing information on solute partitioning, drug permeability, drug intestinal absorption, brain uptake, and skin permeability between different myriad of drugs analyzed in a chromatographic system.

10. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ambudkar et al. (Proc. Natl. Acad. Sci., Vol. 89, pages 8472-5476 (September 1992)) in view of Yang et al. (Advanced Drug Delivery Review, Vol. 23, pages 229-256 (1996)) as applied to claims 1-3, 7, 9, and 10 above, and in further view of Walhagen et al. (Coupled Column Chromatograph- Mass Spectrometry, Journal of Chromatography, 474 (1): 257-263 (1989)).

Ambudkar et al. and Yang et al. have been discussed supra. Ambudkar et al. and Yang et al. differ from the instant invention in failing to teach further characterizing ligands using a mass spectrometer device.

Walhagen et al. teach a coupled-column chromatography-mass spectrometry device focused on applications of immobilized protein phases (see page 258, first full paragraph). Walhagen et al. specifically use alpha-1-acid glycoprotein chiral stationary phase on the column chromatograph (see Summary).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate use of the coupled-column chromatography-mass spectrometry device as taught by Walhagen, into the method of Ambudkar as modified by Yang wherein P-glycoprotein is immobilized into IAM on-line with chromatography

because Walhagen specifically taught applications of immobilized protein phases in alpha-1-acid glycoprotein chiral stationary phase on the column chromatograph; hence, a coupled-column chromatography-mass spectrometry device as taught by Walhagen for application in screening for ligands that manifest themselves as good substrates or bad substrates for P-glycoprotein in immobilized artificial membrane as taught by Ambudkar and incorporated into IAM-chromatography as suggested by Yang should prove useful in further providing information such as molecular weight, etc. in addition to solute partitioning, drug permeability, drug intestinal absorption, brain uptake, and skin permeability between different myriad of drugs as provided by the method taught by Ambudkar and modified by Yang.

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gailene R. Gabel
Patent Examiner
Art Unit 1641
April 26, 2005